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Public Assessment Report

Name of the Product:

Paliperidon ratiopharm

3 mg, 6 mg, 8 mg prolonged-release tablets

(paliperidone)

Procedure number: HU/H/540/001-003/DC

Marketing authorisation holder: Teva Netherlands

Date: 11 December 2019

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets. The holder of the marketing authorisation is Krka d d.

The active substance is paliperidone. Each prolonged-release tablet contains 3 mg, 6 mg or 9 mg paliperidone.

The other ingredients are macrogol, butylhydroxytoluene, povidone, sodium chloride, microcrystalline cellulose, magnesium stearate, iron oxide red (E172), hydroxypropylcellulose and cellulose acetate in the tablet core and hypromellose, titanium dioxide (E171), talc, propylene glycol, iron oxide yellow (E172) (only for 6 mg tablets) and iron oxide red (E172) (only for 9 mg tablets*)* in the coating and shellac, iron oxide black (E172) and propylene glycol in the printing ink.

The 3 mg tablets are white to greyish white round biconvex film-coated tablets with possible uneven surface and imprinted with mark P3 on one side of the tablet. Diameter: approximately 9 mm.

The 6 mg tablets are brownish yellow, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P6 on one side of the tablet. Diameter: approximately 9 mm.

The 9 mg tablets are: off-pink, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P9 on one side of the tablet. Diameter: approximately 9 mm.

The tablets are available in perforated unit dose blisters, in boxes.

The active substance of Paliperidon ratiopharm prolonged-release tablets (further on: Paliperidon ratiopharm), paliperidone belongs to the class of antipsychotic medicines.

Paliperidon ratiopharm is used to treat schizophrenia in adults and in adolescents aged 15 years and older.

Schizophrenia is a disorder with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech, and behaviour and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense.

Paliperidon ratiopharm is also used to treat schizoaffective disorder in adults.

Schizoaffective disorder is a mental condition in which a person experiences a combination of schizophrenia symptoms (as listed above) in addition to mood disorder symptoms (feeling very high, feeling sad,feeling agitated, distracted, sleeplessness, talkativeness, losing interest in

everyday activities, sleeping too much or too little, eating too much or too little, and recurrent thoughts of suicide).

Paliperidon ratiopharm can help alleviate the symptoms of your disease and stop your symptoms from coming back.

What patients need to know before taking Paliperidon ratiopharm

Those who are allergic to paliperidone, risperidone or any of the other ingredients of this medicine, should not take Paliperidon ratiopharm.

Warnings and precautions

Patients should talk to their doctor before taking Paliperidon ratiopharm for
- patients with schizoaffective disorder treated with this medicine should be carefully monitored for a potential switch from manic to depressive symptoms.
- This medicine has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death.

The doctor should be aware if the patient
- have Parkinson's disease or Dementia;
- have ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome);
- have ever experienced abnormal movements of the tongue or face (Tardive Dyskinesia). The patient should be aware that both of these conditions may be caused by this type of medicine. If the patient
- knows that you he/she had low levels of white blood cells in the past (which may or may not have been caused by other medicines);
- is diabetic or prone to diabetes;
- has heart disease or heart disease treatment that makes him/her prone to low blood pressure;
- has epilepsy;
- has a swallowing, stomach or intestinal disorder that reduces your ability to swallow or pass foods by normal bowel movements;
- has diseases associated with diarrhoea,
- has kidney problems;
- has liver problems;
- has prolonged and/or painful erection;
- has difficulty controlling core body temperature or overheating;
- has an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour;
- has or someone else in his/her family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If the patient has any of these conditions, should consult his/her doctor as he/she may want to

adjust the patient's dose or monitor the patient for a while.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in the blood has been seen very rarely with patients taking paliperidone, the doctor may check the patient's white blood cell counts.

Paliperidon ratiopharm may cause the patient to gain weight. Significant weight gain may adversely affect the health. The doctor should regularly measure the patient's body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking paliperidone, the doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of the eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If the patient is planning to have an operation on the eye, he/she should make sure to tell the eye doctor that this medicine is being taken.

Children and adolescents

Paliperidon ratiopharm is not for use in children and adolescents under 15 years for the treatment of schizophrenia.

Paliperidon ratiopharm is not for use in children and adolescents who are under 18 years for the treatment of schizoaffective disorder.

This is because it is not known if paliperidone is safe or effective in these age groups.

Other medicines and Paliperidon ratiopharm

Patients who are are taking, have recently taken or might take any other medicines should consult their doctor.

Abnormalities of electrical function in the heart may occur when this medicine is taken with certain heart medicines that control heart rhythm, or some other types of medicines such as antihistamines, antimalarials, or other antipsychotics.

Since this medicine works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to additive effect on brain function.

Since this medicine can lower blood pressure, care should be taken when this medicine is taken with other medicines that lower blood pressure.

This medicine can reduce the effect of medicines against Parkinson's disease and restless legs syndrome (e.g., levodopa).

The effects of this medicine may be affected if taking medicines that affect the speed of movement in the gut (e.g., metoclopramide).

Dosage reduction for this medicine should be considered when this medicine is co-administered with valproate.

The use of oral risperidone together with this medicine is not recommended as the combination of the two medicines may lead to increased side effects.

Paliperidon ratiopharm with alcohol

Alcohol should be avoided when taking this medicine.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Patients should not take this medicine during pregnancy unless this has been discussed with the doctor. The following symptoms may occur in newborn babies of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If the baby develops any of these symptoms the doctos may need to be contacted.

Driving and using machines

Dizziness and vision problems may occur during treatment with this medicine. This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

Paliperidon ratiopharm contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

How to take Paliperidon ratiopharm

Use in adults

The recommended dose in adults is 6 mg once a day taken in the morning. The dose may be increased or decreased by the doctor within the dose range of 3 mg to 12 mg once a day for schizophrenia or 6 mg to 12 mg once a day for schizoaffective disorder. This depends on how well the medicine works for the patient.

Use in adolescents

The recommended starting dose for treating schizophrenia in adolescents 15 years and older is 3 mg once a day taken in the morning.

For adolescents weighing 51 kg or more the dose may be increased within the range of 6 mg to 12 mg once a day.

For adolescents weighing less than 51 kg the dose may be increased to 6 mg once a day.

The doctor will decide how much to give the patient. The amount the patient takes depends on how well the medicine works for the given patient Paliperidon ratiopharm.

How and when to take Paliperidon ratiopharm

This medicine must be taken by mouth, swallowed whole with water or other liquids. It must not be chewed, broken, or crushed.

This medicine should be taken every morning with breakfast or without breakfast, but in the same way every day. Patients should not alternate between taking this medicine with breakfast one day and without having breakfast the next day.

The active ingredient, paliperidone, dissolves once swallowed and the tablet shell is passed out of the body as waste.

Patients with kidney problems

The doctor may adjust the dose of this medicine based upon the patient's kidney function.

Elderly

The doctor may reduce the dose of medicine if the patient's kidney function is reduced.

What to do if the patients takes more Paliperidon ratiopharm than they should?

The doctor should be contacted right away. The patient may experience sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats.

What to do when taking Paliperidon ratiopharm was forgotten?

No double dose should be taken to make up for a forgotten dose. If one dose is missed, the next dose should be taken on the day following the missed dose. If two or more doses have been missed,the doctor should be contacted.

May taking of Paliperidon ratiopharm be stopped?

Patients should not stop taking this medicine since they will lose its effects. Patients should not stop this medicine unless told to do so by the doctor as the symptoms may return.

Possible side effects

Like all medicines, Paliperidon ratiopharm cause side effects, although not everybody experiences them.

Patients must tell their doctor immediately if they:
- experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If any of these symptoms is noticed, medical advice must be found immediately;
- have dementia and experience a sudden change in the mental state or sudden weakness or numbness of the face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke;
- experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called "Neuroleptic Malignant Syndrome"). Immediate medical treatment may be needed;
- are men and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed;
- experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed;
- experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an 'anaphylactic reaction').

Very common side effects: may affect more than 1 in 10 people
- difficulty falling or staying asleep,
- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face,
- restlessness,
- feeling sleepy or less alert,
- headache.

Common side effects: may affect up to 1 in 10 people
- infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, feeling like having the flu,
- weight gain, increased appetite, weight loss, decreased appetite,
- elated mood (mania), irritability, depression, anxiety,

- dystonia. This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw,
- dizziness,
- dyskinesia. This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching,
- tremor (shaking),
- blurry vision,
- an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, rapid heart rate,
- low blood pressure upon standing (consequently, some people taking Paliperidon ratiopharm may feel faint, dizzy, or may pass out when they stand up or sit up suddenly), high blood pressure,
- sore throat, cough, stuffy nose,
- abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, indigestion, dry mouth, toothache,
- increased liver transaminases in the blood,
- itching, rash,
- bone or muscle ache, back pain, joint pain
- loss of menstrual periods
- fever, weakness, fatigue (tiredness).

Uncommon side effects: may affect up to 1 in 100 people
- pneumonia, infection of the breathing passages, bladder infection, ear infection, tonsillitis,
- white blood cell count decreased, decrease in platelets (blood cells that help stopping bleeding), anaemia, decrease in red blood cells,
- paliperidone can raise the levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include: (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction, (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle,
- diabetes or worsening diabetes, high blood sugar, increased waist size, loss of appetite resulting in malnutrition and low body weight, high blood triglycerides (a fat),
- sleep disorder, confusion, decreased sexual drive, inability to reach orgasm, nervousness, nightmares,
- tardive dyskinesia (twitching or jerking movements that cannot be controlled in the face, tongue, or other parts of the body). The doctor should be informed immediately if the patient experiences involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of Paliperidon ratiopharm may be needed,
- convulsion (fits), fainting, a restless urge to move parts of the body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin,

- oversensitivity of the eyes to light, eye infection or "pink eye", dry eye,
- a sensation of spinning (vertigo), ringing in the ears, ear pain,
- irregular heartbeat, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations),
- low blood pressure,
- shortness of breath, wheezing, nosebleeds,
- swollen tongue, stomach or intestinal infection, difficulty swallowing, excessive passing of gas or wind,
- increased GGT (a liver enzyme called gamma-glutamyltransferase) in the blood, increased liver enzymes in the blood,
- hives (or "nettle rash"), hair loss, eczema, acne,
- an increase of CPK (creatine phosphokinase) in the blood, an enzyme which is sometimes released with muscle breakdown, muscle spasms, joint stiffness, joint swelling, muscle weakness, neck pain,
- incontinence (lack of control) of urine, frequent passing of urine, inability to pass urine, pain when passing urine,
- erectile dysfunction, ejaculation disorder,
- missed menstrual periods or other problems with the cycle (females), leakage of milk from the breasts, sexual dysfunction, breast pain, breast discomfort,
- swelling of the face, mouth, eyes, or lips, swelling of the body, arms or legs,
- chills, an increase in body temperature,
- a change in the way of walking,
- feeling thirsty,
- chest pain, chest discomfort, feeling unwell,
- fall.

Rare side effects: may affect up to 1 in 1,000 people
- eye infection, fungal infection of the nails, infection of the skin, skin inflammation caused by mites,
- dangerously low numbers of a certain type of white blood cell needed to fight infection in the blood,
- decrease in the type of white blood cells that help to protect against infection, increase in eosinophils (a type of white blood cell) in the blood,
- severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure, allergic reaction,
- sugar in the urine,
- inappropriate secretion of a hormone that controls urine volume,
- life threatening complications of uncontrolled diabetes,
- dangerously excessive intake of water, low blood sugar, excessive drinking of water, increased cholesterol in the blood,
- lack of emotion,
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness),
- loss of consciousness, balance disorder, abnormal coordination,
- blood vessel problems in the brain, coma due to uncontrolled diabetes, unresponsive to stimuli, low level of consciousness, shaking of the head,

- glaucoma (increased pressure within the eyeball), increased tears, redness of the eyes, problems with movement of the eyes, eye rolling,
- atrial fibrillation (an abnormal heart rhythm), rapid heartbeat upon standing,
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If any of these symptoms is noticed by the patient, he/she should seek medical advice immediately,
- decreased oxygen in parts of the body (because of decreased blood flow), flushing,
- trouble breathing during sleep (sleep apnea), fast, shallow breathing,
- pneumonia caused by inhaling food, congestion of breathing passages, voice disorder,
- a blockage in the bowels, stool incontinence, very hard stool, lack of bowel muscle movement that causes blockage,
- yellowing of the skin and the eyes (jaundice),
- inflammation of the pancreas,
- serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing,
- thickening of the skin, dry skin, skin redness, skin discolouration, flaky itchy scalp or skin, dandruff,
- breakdown of muscle fibers and pain in muscles (rhabdomyolysis), abnormal posture,
- priapism (a prolonged penile erection that may require surgical treatment),
- development of breasts in men, enlargement of the glands in the breasts, discharge from the breasts, vaginal discharge,
- a delay in menstrual periods, breast enlargement,
- very low body temperature, a decrease in body temperature,
- symptoms of drug withdrawal.

Not known: frequency cannot be estimated from the available data:
- lung congestion,
- increased insulin (a hormone that controls blood sugar levels) in the blood.

The following side effects have been seen with the use of another medicine called risperidone that is very similar to paliperidone, so these can also be expected with Paliperidon ratiopharm: other types of blood vessel problems in the brain and crackly lung sounds. Eye problems during cataract surgery may also occur. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you taking or having taken paliperidone. If the patient needs to have cataract surgery, be sure to tell the eye doctor if this medicine has been taken.

Additional side effects in adolescents

Adolescents generally experienced side effects that were similar to those seen in adults except that the following side effects were seen more commonly:
- feeling sleepy or less alert
- parkinsonism, This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling,

and a loss of expression on the face,
- weight gain,
- common cold symptoms,
- restlessness,
- tremor (shaking),
- stomach pain,
- leaking milk from the breasts in girls,
- breast swelling in boys,
- acne,
- problems with speech,
- stomach or intestinal infection,
- nose bleeds,
- ear infection,
- high blood triglycerides (a fat),
- sensation of spinning (vertigo).

How to store Paliperidon ratiopharm

It should be stored in the original package in order to protect from moisture and kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Paliperidon ratiopharm 3 mg, 6 mg, 9 mg prolonged-release tablets. The procedure was finalised at 11 March 2018. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Belgium, Italy and Spain) concerned the generic version of paliperidone 3 mg, 6 mg and 8 mg prolonged-release tablets (Paliperidon ratiopharm tablets).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator (and reference) product was Invega® prolonged-release tablets by Janssen-Cilag International NV. Paliperidone was first approved in the Community in 2007 *via* centralised procedure.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets (Teva Netherlands).

The products are indicated for the treatment of schizophrenia in adults and adolescents 15 years and older and for the treatment of schizoaffective disorder in adults.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

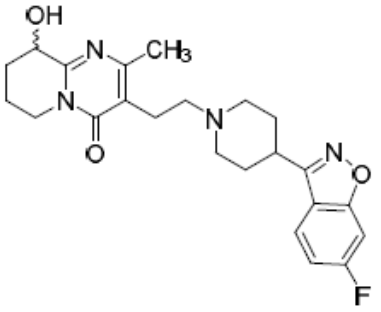
This chemical-pharmaceutical assessment report concerns the application of Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e. generic application). The reference products are Invega 3 mg, 6 mg and 9 mg prolonged-release tablets (containing 3, 6 and 9 mg paliperidone as active ingredient, respectively) which were the original products of Janssen-Cilag International NV.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non-proprietary name INN: paliperidone
Chemical name: (9*RS*)-3-[2-[4-(6-Fluoro-1, 2-benzisoxazol-3-yl)piperidin-1-yl]]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4*H*-pyrido [1,2-a]pyrimidin-4-one

Structure:



The drug substance is a white to yellow powder. It is slightly soluble in methanol, sparingly soluble in methylene chloride and practically insoluble in water. Paliperidone is a chiral molecule containing one asymmetric carbon atom; the manufacturing process produces racemic mixture. The substance exhibits polymorphism. It has been proved that the manufacturer consistently manufactures the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the drug substance is adequate.

Evidence of the structure has been confirmed by ^{1}H- and ^{13}C-NMR, MS, IR, DSC and XRD spectroscopy. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Paliperidone is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the drug substance, which includes the following tests: identification, solubility, related substances, assay, water content, sulphated ash, residual solvent, and microbiological quality.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (ICH) Q6A guideline. The limits set are properly justified.

Testing methods not described in details in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period of is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the drug substance manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop prolonged-release formulation that would be essentially similar to the reference product Invega® that are based on the OROS® (Oral Osmotic System) system.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained:

> 3 mg: white to greyish white round biconvex film-coated tablets with possible uneven surface and imprinted with mark P3 on one side of the tablet. Diameter: approximately 9 mm.

6 mg: brownish yellow, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P6 on one side of the tablet. Diameter: approximately 9 mm.

9 mg: off-pink, round, biconvex, film-coated tablets with possible uneven surface and imprinted with mark P9 on one side of the tablet. Diameter: approximately 9 mm.

The excipients used in the core of finished product are macrogol, butylhydroxytoluene, povidone, sodium chloride, microcrystalline cellulose, magnesium stearate, red iron oxide (E172), hydroxypropylcellulose and cellulose acetate. The coating of the tablet consists of hypromellose, titanium dioxide (E171), talc, propylene glycol, and iron oxide yellow (E172) – *only for 6 mg tablets* or red (E172) – *only for 9 mg tablets*. The printing ink contains shellac, black iron oxide (E172) and propylene glycol.

All excipients used comply with their respective Ph. Eur. monograph except for the iron oxide (which complies with the Commission Regulation (EU) No. 231/2012.). Compliance of the product with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence studies are presented.

Paliperidon ratiopharm prolonged-release tablets are packed in OPA/Al/PVC//Al blisters and box. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years is approved with the following storage condition: “Store in the original package in order to protect from moisture”.
.
The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets have been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of paliperidone are well known. As paliperidone is a widely used, well-known active substance, no further studies are required and the applicant provided none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient.

III.2 Pharmacology

Paliperidone (9-hydroxy-risperidone) is the major active metabolite of resperidone in all laboratory animal species as well as in humans. Paliperidone and risperidone have very similar pharmacologic profile and exhibit the characteristic of an atypical antipsychotic.

Paliperidone is a receptor monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5-hydroxytryptamine [5-HT] type 2A [5- HT2A]) antagonism of antipsychotic drugs.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of paliperidone.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment

Since Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of paliperidone are well-known. As Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets is a generic product there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of paliperidone is well known.

Except for showing bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption: following a single dose, paliperidone exhibits a gradual ascending release rate, allowing the plasma concentrations of paliperidone to steadily rise to reach peak plasma concentration (C_{max}) approximately 24 hours after dosing. With once-daily dosing of paliperidone, steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

Paliperidone is the active metabolite of risperidone. The release characteristics of paliperidone prolonged-release tablets result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone (fluctuation index 38% versus 125%).

The absolute oral bioavailability of paliperidone following administration is 28% (90% CI of 23%-33%).

Administration of paliperidone prolonged-release tablets with a standard high-fat/high-caloric meal increases C_{max} and AUC of paliperidone by up to 50-60% compared with administration in the fasting state.

Distribution: paliperidone is rapidly distributed. The apparent volume of distribution is 487 l. The plasma protein binding of paliperidone is 74%. It binds primarily to α_1-acid glycoprotein and albumin.

Biotransformation and *elimination*: one week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised by the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified in vivo, none of which

accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. The terminal elimination half-life of paliperidone is about 23 hours.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

IV.2.2 Bioequivalence studies

Five) pivotal bioequivalence studies have been reported in the submitted dossier in order to support essential similarity between paliperidone 6 mg (fed, single dose), paliperidone 3 mg (fasting, single dose), paliperidone 6 mg (fasting, multiple dose) and paliperidone 9 mg (fasting and fed single dose) prolonged-release tablets (test products) and Invega® 6 mg, 3 mg, 6 mg and 9 mg prolonged-release tablets (manufactured by Janssen-Cilag SpA, Italy (reference product), respectively, in healthy adult subjects according to the bioequivalence guideline in force (CPMP/EWP/QWP/1401/98/ Rev 1/Corr** 2010).

The applicant declared that the bioequivalence studies had been performed in accordance with GCP requirements.

Biowaiver

The applicant claimed for biowaiver for the dose strengths of 6 mg in fasting state as well as 3 mg and 9 mg both in fed and multiple dose (fasting state) on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) the three different dose-strength tablets, i.e. 3 mg, 6 mg and 9 mg of the proposed pharmaceutical products are manufactured by the same manufacturer using the same manufacturing process;
b) the qualitative composition of the claimed strengths is the same;
c) the quantitative compositions of the claimed strengths are proportionally similar;
d) *in vitro* dissolution data (covering the pH range of 1.2 - 6.8) confirmed the similarity between the claimed strengths;
e) pharmacokinetics of orally administered paliperidone is linear in the claimed therapeutic range (3 - 9 mg).

The biowaiver claim for the 3 mg and 9 mg (in fed state and in multiple dose, fasting state), and 6 mg (in fasting state) dose strengths is justified.

Bioequivalence study with the 6 mg strength, single dose, fed state

The main objective of this study was to compare the rate and extent of absorption of the test- and reference products administered to healthy adult volunteers in a single dose under fed conditions. The reference drug can be taken with- or without food according to its Summary of Products Characteristics.

It was an open label, two-period, two-sequence, two-way crossover, randomized, single dose bioequivalence study of paliperidone 6 mg prolonged-release tablets (test formulation) versus equal dose of the reference formulation (Invega® 6 mg prolonged-release tablets) in healthy male volunteers under fed conditions

Subjects were administered the test- and reference medications (as per the randomisation scheme) as a single oral dose of 1 prolonged-release tablet with room temperature, still bottled water in sitting posture after at least 10 hours fasting, and 30 minutes after a high-fat high-calories breakfast served to the volunteers, in each study period.

Blood samples were taken at suitable intervals and analysed for paliperidone content.

The following pharmacokinetic parameters were calculated:

- primary: AUC_{0-t}, C_{max}
- other: T_{max}, AUC_{0-inf}, $t_{1/2}$, MRT, %extraAUC.

The following statistical methods were used in evaluations

- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for Test- and Reference pharmacokinetic data using non-compartmental model and using SAS® version 9.4.
- Log-transformation of AUC_{0-inf_pred}, AUC_{0-t} and C_{max} data.
- Evaluation of data using a linear mixed-effects model (SAS® Version 9.4, SAS Institute Inc., USA), with the main effects of *treatment*, *period*, *sequence* and *subject nested within sequence* in ANOVA (PROC GLM of SAS®).
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level).
- Applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon Signed-Rank test).
- Descriptive statistics of safety data collected during the whole study period.

The test product can be considered bioequivalent to the reference product when the ln-transformed test/reference LS (least-squares) mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00 %.

The results are shown in the next Table:

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$ (pg·hr/mL)	99.566%	90.14% - 109.97%	35.528
$AUC_{(0-inf)}$ (pg·hr/mL)	99.296%	89.95% - 109.62%	35.332
Cmax (pg/mL)	101.186%	91.25% - 112.20%	37.020

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Bioequivalence was met for the primary pharmacokinetic parameters in this study.

Safety results: no death, serious or life-threatening adverse events) occurred during the study. No subject was withdrawn from the study for safety reason. No new safety concerns were raised during the conduct of the study. The test- and reference product were comparable in their safety and tolerability.

Overall, the drugs investigated were well tolerated by all subjects included in the study.

On the basis of results obtained in the study, a single dose of the test formulation (6 mg paliperidone) is judged to be bioequivalent to a single dose of the reference product (6 mg paliperidone) under fed conditions.

Bioequivalence study with the 3 mg strength (single dose, fasting)

The main objective of this study was to compare the rate and extent of absorption of the Test- and Reference products administered to healthy adult volunteers in a single dose under fasting conditions.

It was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-sequence bioequivalence study of paliperidone with adequate washout period between the two periods, in healthy adult male subjects under fasting condition.

The subjects were administered the test- and reference medications (as per the randomisation scheme) as a single oral dose of 1 prolonged-release tablet of 3 mg paliperidone with 200 mL of room temperature, still bottled water in sitting posture after at least 10 hours fasting in fasting conditions, in each study period.

Blood samples taken at suitable intervals and analysed for paliperidone.

- The following pharmacokinetic parameters were calculated:
- primary: AUC_{0-t}, C_{max}
- other: T_{max}, $AUC_{0-\infty}$, T_{half}, λ_z, Residual area (%),

The following statistical methods were used in the evaluations:

- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test- and reference pharmacokinetic data using non-compartmental model and using SAS® version 9.4,
- Log-transformation of $AUC_{0\text{-}inf\_pred}$, $AUC_{0\text{-}t}$ and C_{max} data,
- Evaluation of data using a linear mixed-effects model (SAS® Version 9.4, SAS Institute Inc., USA), with the main effects of *treatment*, *period*, *sequence* and *subject nested within sequence* in ANOVA (PROC GLM of SAS®),
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level),
- Applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon Signed-Rank test),
- Descriptive statistics of safety data collected during the whole study period.

The test product can be considered bioequivalent to the reference product when the ln-transformed test/reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00%.

The results are summarised in the Table below.

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV%[1]
$AUC_{(0\text{-}T)}$	105.55	92.39 - 120.57	45.9
$AUC_{(0\text{-}inf)}$	105.37	92.36 - 120.21	45.4
C_{max}	106.42	92.76 - 122.09	48.0

[1] Estimated from the Residual Mean Squares

Bioequivalence was met for the primary pharmacokinetic parameters in this study.

No death or life-threatening adverse events occurred during the study. The incidence of drug-related adverse events was similar for both the test and reference. No new safety concerns were raised during the conduct of the study.

On the basis of results obtained in this study, a single dose of the test formulation (3 mg paliperidone) is judged to be bioequivalent to a single dose of the reference product under fasting conditions.

Bioequivalence study with the 6 mg strength, multiple dose, fasting conditions

The main objective of this study was to compare the rate and extent of absorption of the Test- and Reference products administered to healthy adult volunteers in multiple dose under fasting conditions.
It was an open label, two-period, two-sequence, two-way crossover, randomized, multiple dose bioequivalence study of paliperidone 6 mg prolonged-release tablets (test

formulation) *versus* equal dose of reference formulation (Invega® 6 mg prolonged-release tablets) in healthy male volunteers under fasting conditions

Subjects were administered the test- and reference medications (as per the randomisation scheme) as multiple oral doses of prolonged-release tablets with 200 mL of room temperature, still bottled water in sitting posture after at least 10 hours fasting, in each study period. In both periods of the study subjects received 07 doses of study medications

Blood samples taken at suitable intervals and analysed for paliperidone.

The following pharmacokinetic parameters were calculated:

- primary: $AUC_{0\text{-}tau}$ $C_{max.ss,}$ $C_{min.ss}$
- other: $T_{max.ss}$, C_{av}, %Fluctuation, C_{pd} (pre-dose concentration).

The following statistical methods were used in the evaluations:

- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for test- and reference pharmacokinetic data using non-compartmental model and using SAS® version 9.4,
- Log-transformation of $AUC_{0\text{-}tau}$, $C_{max.ss}$, $C_{min.ss}$ data,
- Evaluation of data using a linear mixed-effects model (SAS® Version 9.4, SAS Institute Inc., USA), with the main effects of *treatment*, *period*, *sequence* and *subject nested within sequence* in RMANOVA (repeated measure, three consecutive C_{pd} were used, PROC GLM of SAS®),
- Helmert's contrast analysis in determination of achievement of steady state,
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level),
- Applying non-parametric analysis of $T_{max.ss}$ on untransformed data (Wilcoxon Signed-Rank test),
- Descriptive statistics of safety data collected during the whole study period.

The test product can be considered bioequivalent to the reference product, when the ln-transformed test/reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00 %.

The results are summarised in the Table below.

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0\text{-}tau)}$	98.75 %	90.99% - 107.18%	27.8
$C_{max.ss}$	105.27 %	97.16% - 114.07%	27.2
$C_{min.ss}$	93.86 %	84.67% - 104.05%	35.4

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Bioequivalence was met for the primary pharmacokinetic parameters in this study.

No death, serious or life-threatening adverse events occurred during the study. No new safety concern was identified.

On the basis of results obtained in this study the test formulation (6 mg paliperidone) is judged to be bioequivalent to the reference product after multiple-dose administration in steady state, under fasting conditions.

Bioequivalence study with the 9 mg strength, single dose, fasting)

The main objective of this study was to compare the rate and extent of absorption of the test- and reference products administered to healthy adult volunteers in a single dose under fasting conditions.

The design of this investigation was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-sequence bioequivalence study of paliperidone with a suitable washout period between the two periods, in healthy adult male subjects under fasting condition. The test product was paliperidone 9 mg prolonged-release tablets, the reference product Invega® 9 mg prolonged-release tablets

The subjects were administered the test- and reference medications (as per the randomisation scheme) as a single oral dose of 1 prolonged-release tablet with 200 mL of room temperature, still bottled water in sitting posture after at least 10 hours fasting, in fasting conditions, in each study period.

Blood samples taken per period at suitable intervals and analysed for paliperidone.

The following pharmacokinetic parameters were calculated:
- primary: $AUC_{0\text{-}t}$, C_{max}
- other: T_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$, MRT, %extraAUC.

The following statistical methods were used in the evaluations:
- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for Test- and Reference pharmacokinetic data using non-compartmental model and using SAS® version 9.4,
- Log-transformation of $AUC_{0\text{-}inf\_pred}$, $AUC_{0\text{-}t}$ and C_{max} data,

- Evaluation of data using a linear mixed-effects model (SAS® Version 9.4, SAS Institute. Inc., USA), with the main effects of *treatment*, *period*, *sequence* and *subject nested within sequence* in ANOVA (PROC GLM of SAS®),
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level).
- Applying non-parametric analysis of T_{max} on untransformed data (Wilcoxon Signed-Rank test),
- Descriptive statistics of safety data collected during the whole study period.

Test product can be considered bioequivalent to the reference product, when the ln-transformed test/reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00 %.

The results are summarised in the Table below.

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-t)}$	98.43 %	89.26% - 108.55%	38.0
$AUC_{(0-inf)}$	98.74 %	89.55% - 108.87%	37.9
C_{max}	100.81 %	91.51% - 111.04%	37.5

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares.

Bioequivalence was met for the primary pharmacokinetic parameters in this study.

No death, serious or life-threatening adverse events occurred during the study. No subject was withdrawn from the study for safety reason. The test- and reference product were comparable in their safety and tolerability. No new safety concern was identified.

On the basis of results obtained in this study, a single dose of the test formulation (9 mg paliperidone) is judged to be bioequivalent to a single dose of the Reference product under fasting conditions.

Bioequivalence study with the 9 mg strength, single dose, fed

The main objective of this study was to compare the rate and extent of absorption of the test- and reference products administered to healthy adult volunteers in a single dose under fed conditions.

The design of this investigation was a single-dose, randomized, open-label, laboratory blind, crossover, two-sequence bioequivalence study of paliperidone 9 mg prolonged-release tablets (test formulation) and Invega® 9 mg prolonged-release tablets (reference formulation) with a suitable washout period between the two periods, in healthy adult male subjects under fed condition.

The subjects were administered the test- and reference medications (as per the randomisation scheme) as a single oral dose of 1 tablet with approximately 200 mL of room temperature water under fed conditions.

Blood samples were taken and analysed for paliperidone.

The pharmacokinetic parameters and statistical methods applied were as follows.

Pharmacokinetic parameters:
- primary: AUC_t, C_{max}
- other: T_{max}, AUC_{inf}, $T_{1/2}$, λ.

Statistical methods:
- Descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric least squares means for test- and reference pharmacokinetic data using non-compartmental model and using SAS® (SAS Institute Inc. USA) version 9.4,
- Log-transformation of $AUC_{0\text{-}inf}$, $AUC_{0\text{-}T}$ and C_{max} data.
- Evaluation of data using a linear mixed-effects model (SAS®), with the main effects of *treatment*, *period*, *sequence* and *subjects nested within sequence* in ANOVA,
- Calculation of 90% confidence intervals for the difference between the least square means (LSM) for primary parameters (LSMEANS, GLM procedures of ANOVA at $\alpha = 0.05$ significance level),
- Applying non-parametric analysis of T_{max} on untransformed data,
- Descriptive statistics of safety data collected during the whole study period.

The test product can be considered bioequivalent to the reference product, when the ln-transformed test/reference least-squares mean ratios and their 90% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 - 125.00% for paliperidone.

The results are summarised in the Table below.

Pharmacokinetic parameter	**Geometric Mean Ratio Test / Reference**	**Confidence Intervals**	**CV%**
AUC_t	97.77	88.97 - 107.45	36.51
AUC_{inf}	97.72	88.88 - 107.43	36.69
C_{max}	96.63	87.04 - 107.26	40.71

Safety results: no death, serious or life-threatening adverse events (AEs) occurred during the study. No serious adverse event were reported. The test- and reference products exhibited comparable tolerability. No new safety concern was identified.

In this study bioequivalence was demonstrated between paliperidone 9 mg prolonged-release tablets (test) and Invega® 9 mg prolonged-release tablets (reference), in healthy male volunteers under fed conditions.

Moreover, the applicant has submitted detailed description of the simulation study performed to simulate multiple-dose conditions on the 9 mg dose strength of paliperidone *in vivo*.

Taking into account that the applicant

- has performed a successful multiple-dose bioequivalence study with 6 mg dose strength, and
- paliperidone pharmacokinetics are linear in the claimed dose-strength interval (3 – 9 mg) for both the test- and reference products, and
- the formulation gives an additional assurance for validity of extrapolations, and
- results of the simulation study (as supportive information) are acceptable,

no multiple-dose in vivo (bioequivalence) study with the 9 mg dose strength is required.

Conclusion on bioequivalence studies

The results of the above five bioequivalence studies give convincing assurance that the test products, paliperidone 3 mg, 6 mg and 9 mg prolonged-release tablets are bioequivalent to the reference medicine, Invega®3 mg, 6 mg and 9 mg prolonged-release tables.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets were not needed and not performed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate literature review to describe the efficacy profile of paliperidone.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

The applicant has provided an adequate literature review to describe the safety profile of paliperidone.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The applicant has submitted a signed Summary of the applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns

Important identified risks	Cerebrovascular accident
Important potential risks	Carcinogenicity (pituitary adenomas, endocrine pancreas tumours, breast cancer)
	Overall increased mortality in elderly patients with dementia
	Cerebrovascular adverse events in elderly patients with dementia
	Cognitive and motor impairment
	Suicidality
	Depression in patients with affective disorders
	Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy bodies
	Gastrointestinal obstruction (in patients with pre-existing severe gastrointestinal narrowing [pathologic or iatrogenic] or in patients with dysphagia or significant difficulty in swallowing tablets)
	Decreased bone mineral density/osteoporosis
	Accidental exposure to product by child
Missing information	Use in haemodialysis patients
	Exposure during pregnancy
	Exposure via breastfeeding

Pharmacovigilance plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to the prolonged-release tablets containing paliperidone. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in the Summary of Product Characteristics, Package Leaflet and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to the prolonged-release tablets containing paliperidone. No additional activities are proposed. For any further information on risk minimisation refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

This application concerns a generic product. Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

To support the application the Applicant has adequately demonstrated bioequivalence between Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets and the reference product Invega® 3 mg, 6 mg and 9 mg prolonged-release tablets.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Paliperidon ratiopharm 3 mg, 6 mg and 9 mg prolonged-release tablets, generic versions of palipredone. The future holder of authorisation is Teva Netherlands.

The indication is treatment of schizophrenia in adults and adolescents 15 years and older and for the treatment of schizoaffective disorder in adults.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Invega® prolonged-release tablets by Janssen-Cilag International NV. The applicant has adequately demonstrated bioequivalence between the product and reference medicine.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Paliperidon ratiopharm 3 mg, 6 mg and 9 mg controlled-release tablets.

V.2 Classification

Prescription only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
Repeat-use procedure involving new CMSs Austria, Greece, Netherlands and Portugal	HU/H/0540/001-003/E/001	no	16. 10. 2018	15. 12. 2018	approval	no
Changes in the safety information following a referral procedure	001-003/IB/002/G	yes	05. 02. 2019	07. 03. 2019	approval	no